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## PROSTATIC CANCER PRESENTING MONOCLONAL GAMMOPATHY: REPORT OF TWO CASES

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Two cases of prostatic cancer accompanied by monoclonal gammopathy of undetermined significance (MGUS) are reported. Both cases presented IgG- $\lambda$  type hyperimmunoglobulinemia and Bence Jones protein (BJP) in the urine. A characteristic of both cases was significant multiple bone metastasis, and one case also demonstrated a severe immunological disorder. During the treatment, one patient recovered from MGUS. We recommend that elderly male patients manifesting MGUS be examined for prostatic cancer.

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**Key words:** Prostatic cancer, Monoclonal gammopathy, Bence Jones protein

### INTRODUCTION

Monoclonal gammopathy of undetermined significance (MGUS) is a disorder due to the proliferation of a single clone of the plasma cells. The condition reportedly may be caused by an autoimmune disease, chronic infection, a state of immunodeficiency, liver disease and malignancy<sup>1)</sup>. MGUS is reported to be present in 0.9% of the normal adult population, with this incidence increasing to 3% among individuals more than 70 years old<sup>2,3)</sup>. Three (5%) of 66 consecutive patients exhibiting BJP proteinuria were classified as having MGUS<sup>4)</sup>. The concentration of the monoclonal protein in MGUS is almost less than 3  $\mu$ g per 100 ml, and the immunoglobulins other than this usually are not suppressed<sup>4-6)</sup>. Although the pathogenetic mechanism of MGUS is not clear, cancer or chronic inflammation stimulates proliferation of a single clone of a plasma cell and leads to MGUS<sup>1)</sup>. Aging and cancer have also been suggested to cause immune disorders which may lead to MGUS. Herein, we report two cases of prostatic cancer presenting MGUS. It was characteristic that one case showed severe immunosuppression.

### CASE REPORT

**Case 1.** An 81-year-old male presented himself with a high fever. The laboratory data revealed high levels of lactate dehydrogenase (LDH; 699 U/l) and alkaline phosphatase (Alp; 1,015 mU/ml) in addition to hyperimmunoglobulinemia (Fig. 1A). Immunoelectrophoresis of serum revealed an M band suggesting IgG- $\lambda$  type of M-protein, and Bence Jones protein (B-

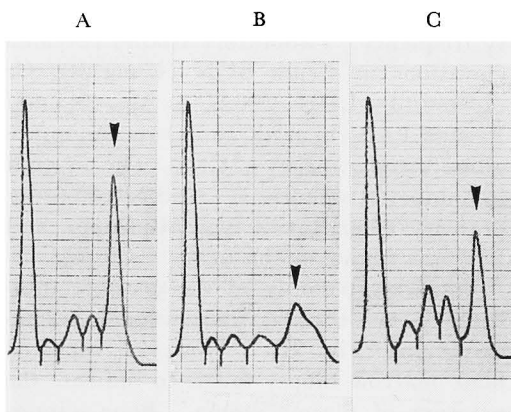


Fig. 1. Serum protein fractions in case 1 (A,B) and case 2 (C). Arrow indicates monoclonal band of immunoglobulin. Case 1 patient showed monoclonal gammopathy at admission (A), but had recovered after 4 months of treatment (B).

JP) was identified in his urine. The IgG, IgA and IgM contents of serum were 3,308 292 and 126 mg/dl, respectively. A bone marrow biopsy specimen revealed reactive plasmacytosis (bone marrow plasma cells; 8.8%). A general bone survey indicated a focal osteoblastic region, but failed to reveal either a region of bone lysis or generalized osteoporosis. Bone scintigraphy revealed multiple hot spots. These findings were not characteristic of multiple myeloma.

A stone-hard prostate and the high level of serum prostate acid phosphatase (PAP; 218 ng/ml) indicated prostatic cancer with multiple bone metastasis. The T4/T8 lymphocyte ratio was a low 0.35 (normal 1.18 to 2.08), indicating a severe immunosuppression. The patient underwent castration and was administered transorally 300 mg of diethylstilbestrol phosphate (DES) following transrectal biopsy of the prostate.

Histological examination demonstrated moderately differentiated adenocarcinoma in the prostate (Fig. 2A). The patient's body temperature rose during treatment, and was lowered not by antibiotics but by immunoglobulin. Improvement of the hyperimmunoglobulinemia was registered after four months of treatment (Fig. 1B). However, the patient died of prostration and cachexia.

**Case 2.** An 88-year-old male presented himself with anorexia and nocturnal urinary frequency. Laboratory studies revealed elevations in serum BUN (47 mg/dl), Cr (2.6 mg/dl), LDH (506 U/l), Alp (615 mU/l), and PAP (15 ng/dl), and hyperimmunoglobulinemia (Fig. 1C). The serum immunoelectrophoresis indicated the presence of an IgG- $\lambda$  type M-protein, and BJP was found in the urine.

Transrectal biopsy of the prostate indicated a moderately differentiated adenocarcinoma (Fig. 2B). However, repeated bone marrow biopsy failed to indicate the presence of plasmacytoma. Bone scintigraphy demonstrated a multiple radioisotope uptake, suggesting multiple metastasis of the prostatic cancer. The patient was subjected to castration and subsequently administered transoral 300 mg of

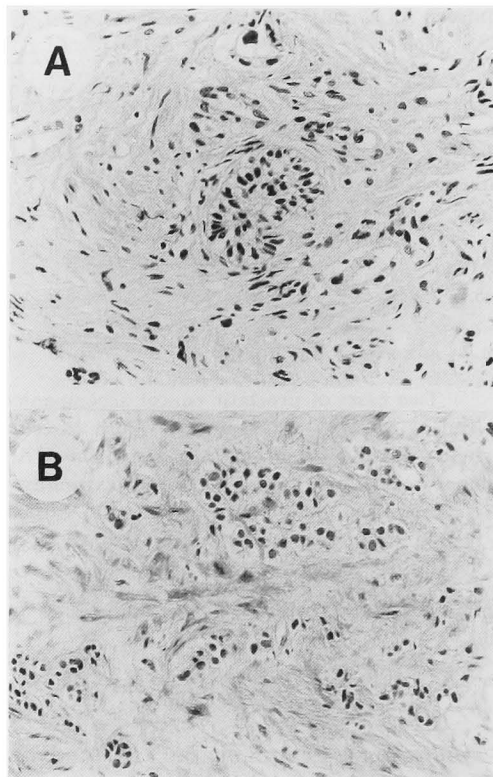


Fig. 2. The histological findings of prostate in case 1 (A) and case 2 (B). H & E staining ( $\times 100$ ).

DES. BJP proteinuria persisted and dyspnea accompanied by pleural effusion occurred 18 months postoperatively. Aspiration of the pleural fluid and pleural biopsy confirmed the presence of adenocarcinoma, indicating the pleural metastasis of the prostatic cancer. The patient died from respiratory failure two years after treatment.

Post-mortem examination revealed adenocarcinoma infiltration of bone marrow tissue, but not plasma cells. There was cancer cell infiltration of the pleural wall, which mediated the massive pleural effusion. An adenocarcinoma was also identified in the prostate. The diagnosis essentially was MGUS accompanying prostatic cancer which metastasized to the bone and pleura.

## DISCUSSION

MGUS refers to a condition in which monoclonal protein is present but not

associated with myeloma, amyloidosis, macroglobulinemia or a malignant lymphoproliferative process. It is well known to increase in incidence with age<sup>7)</sup>. A difference in incidence by race also has been reported. Blacks had a two times higher incidence of MGUS than whites<sup>8)</sup>. Malignancy in MGUS ranges from 7 to 14.8 percent<sup>5, 9)</sup>, and the prevalence of the different types of tumors associated with MGUS is variable<sup>7)</sup>. Few reports discuss the prognosis of the malignancy showing MGUS, but MGUS must be followed up indefinitely, because such reported long-term follow-ups have indicated the development of myeloma in 22% of the cases, and of macroglobulinemia in 3 % of the cases<sup>10)</sup>. Four cases of prostatic cancer associated with MGUS have been described in previous reports<sup>7, 9, 11)</sup>. However, detailed explanations were not provided. Prostatic cancer is the most common cancer which metastasizes to bone. It is speculated that either direct or indirect stimulation of plasma cells by the metastatic bone tumor leads to MGUS.

An immune disorder also has been reported to cause MGUS<sup>1)</sup>. In case 1, decrease in the T4/T8 lymphocyte ratio indicates severe immunosuppression. In this case, the fever lowered by the administration of immunoglobulin was presumed to have been caused by interleukine 1 mediated from active macrophage by excess antigen stimulation of a cancer, because the administration of immunoglobulin may block macrophage complement receptors. Prostatic cancer belongs to the high risk group demonstrating MGUS, because it tends to metastasize to the bone and invade the bone marrow. In conclusion, we recommend an examination for prostatic cancer in elderly male patients with MGUS.

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## 和文抄録

## 単クローン性形質細胞増多症を示した前立腺癌の2例

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われわれは単クローン性形質細胞増多症（MGUS）を示した前立腺癌を2例経験した。2例とも IgG- $\lambda$  タイプの MGUS であり、尿中にベンスジョーンズ蛋白が認められた。2例を通して特徴的なことは多発性の骨転移が認められたことであった。1例は著じる

しい免疫不全状態を示し、治療によって MGUS の改善が認められた。高齢の男性で MGUS を示した症例は、前立腺癌の可能性を一度考える必要があると思われた。

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